or in any one of the B', I, or D strands of the back β-sheet, or in any one of the connecting loops and in any one of the B', I, or D strands of the back β-sheet, and which substitution leads to inactivation of the biological activity of human TNFα.

78 The human TNFα molecule according to claim 77, wherein the substitution does not comprise any complete strand of the back β-sheet.

79. The human TNFα molecule according to claim 77, wherein the substitution has been made in regions of the TNFα molecule so as to essentially preserve the β-sheet structure of the B and G strands.

80. The human TNFα molecule according claim 77, wherein the substitution comprises at least a segment of the H strand of the front β-sheet and of the connecting loop to the I strand of the back β-sheet, a segment of the H and I strands and the entire connecting loop, a segment of the D strand of the back β-sheet and at least a segment of the E strand of the front β-sheet and the entire connecting loop, the entire C' and C strands of the front β-sheet and a segment of the D strand of the back β-sheet, or at least a segment of the E strand of the front β-sheet and of one or both the connecting loops.

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81. The human TNFα molecule according to claim 77, wherein the substitution has been made in regions of the TNFα molecule which involves the strands of the front β-sheets and/or the connecting loops so as to essentially preserve the β-sheet structure of any of the strands of the back β-sheet.

82. The human TNFα molecule according to claim 80, wherein the substitution has been made in regions of the TNFα molecule, which involve a segment of the D strand of the back β-sheet.

83. The human TNFα molecule according to claim 80, wherein the substitution comprises at least a segment of the H strand of the front β-sheet and of the connecting loop to the I strand.

84. The human TNFα molecule according to claim 80, wherein the substitution comprises segments of the H and I strands and the entire connecting loop.

85. The human TNFα molecule according to claim 80, wherein the substitution comprises a segment of the D strand, at least a segment of the E strand and the entire connecting loop.

86. The human TNFα molecule according to claim 80, wherein the substitution comprises the entire C' and C strands and a segment of the D strand.

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87. The human TNFα molecule according to claim 80, wherein the substitution comprises at least a segment of the E strand and of the front β-sheet of one or both of the connecting loops.

88. The TNFα molecule according to claim 77, wherein when said modified TNFα molecule is tested for biological activity in the L929 bioassay, it is substantially free from TNFα activity.

89. The TNFα molecule according to claim 77, wherein neutralizing antibodies raised against said modified TNFα molecule in a suitable host is able to significantly inhibit the activity of native TNFα in the L929 bioassay, and/or wherein said antibodies significantly inhibit the binding of wild-type human TNFα to the 55 kD TNFα receptor 1 (TNFα-R55) or the to the 75 kD TNFα receptor (TNFα-R75).

90. The human TNFα molecule according claim 77, wherein the inserted T cell epitope is promiscuous and known to be immunogenic in a majority of human HLA class II types.

91. The human TNFα molecule according to claim 90, wherein the epitope is derived from Tetanus toxoid.

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92. The human TNFα according to claim 91, having the amino acid sequence shown in SEQ ID NO:8.

93. The human TNFα according to claim 91, having the amino acid sequence shown in SEQ ID NO:10.

94. The human TNFα molecule according to claim 91, having the amino acid sequence shown in SEQ ID NO:4 or SEQ ID NO:16.

95. The human TNFα according to claim 91, having the amino acid sequence shown in SEQ ID NO:20.

96. The human TNFα according to claim 91, having the amino acid sequence shown in SEQ ID NO:14.

97. Dimers, oligomers or multimers of the human TNFα molecule according of claim 77.

98. An isolated DNA molecule that codes for a human TNFα molecule according of claim 77.

99. A vector which comprises the isolated DNA molecule according to claim 98.

#1 100. An expression vector, which comprises the isolated DNA molecule according to claim 98 operatively linked to an expression control sequence.

101. A host, which is transformed with the expression vector of claim 100.

102. A host according to claim 101, which host is a strain of bacteria or fungi or an insect, mammalian, or avian cell line.

103. A method of producing a human TNFα molecule comprising growing the host cells of claim 101 under suitable conditions permitting production of the human TNFα and recovering the human TNFα so produced.

104. The human TNFα molecule according to claim77 in the form of a fusion protein with an adjuvant molecule.

105. A vaccine against TNFα, comprising an immunogenic amount of one or more human TNFα molecules according to claim 77 in combination with a pharmaceutically acceptable excipient and optionally a pharmaceutically acceptable adjuvant.

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106. A vaccine according to claim 105 for the prevention or treatment of diseases promoted by TNFα release or activity.

107. A vaccine against TNFα comprising isolated DNA coding for the human TNFα molecule according to claim 77 inserted in an expression vector.

108. A vaccine according to claim 107 containing a construct comprising a non-infectious non-integrating DNA sequence encoding the human TNFα molecule according to claim 77 operatively linked to a promoter sequence that controls the expression of said DNA sequence in humans, in an amount sufficient that uptake of said construct occurs, and sufficient expression occurs to induce a neutralizing antibody response against TNFα.

109. A vaccine according to claim 107, wherein the expression vector is a viral expression vector.

110. A vaccine according to claim 105 formulated for oral or parenteral administration.

111. A method comprising raising antibodies against a human TNFα molecule by administering to a human the a vaccine as defined in claim 105 and using the antibodies in a diagnostic in vitro test for TNFα.

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112. In a diagnostic in vitro method of using antibodies raised against a human TNFα molecule, the improvement wherein the TNFα molecule is the human TNFα molecule according to claim 77.

113. A method of testing human body fluids for the presence of TNFα which comprises contacting a composition containing antibodies raised against the human TNFα molecule according to claim 77 with a sample of human body fluid and determining whether said antibodies bind to TNFα in said sample.

114. A method for diagnosing TNFα-related diseases employing an in vitro immunoassay to detect TNFα in human body fluids.

115. The method of claim 113 wherein the testing uses a sandwich assay or ELISA assay, unamplified or amplified.

116. A method of manufacture of a medicament for the treatment or prevention of diseases in human beings, the pathophysiology of which is at least partially due to TNFα release or activity, comprising combining an effective amount of at least one human TNFα molecule according to claim 77 with pharmaceutically acceptable a adjuvant or carrier molecule.

#1 117. The human TNFα molecule according to claim 104, wherein the adjuvant molecule is an immunologically active adjuvant.

118. The human TNFα molecule according to claim 104, wherein the adjuvant molecule is GM-SCF, HSP70, or interleukin.

119. A vaccine according to claim 105, wherein the pharmaceutically acceptable adjuvant is aluminum phosphate, aluminum hydroxide, calcium phosphate, muramyl dipeptide, or iscom.

120. A vaccine according to claim 106, wherein the diseases are chronic inflammatory diseases, cancer, disseminated sclerosis, diabetes, psoriasis, osteoporosis, or asthma.

121. A vaccine according to claim 120, wherein the chronic inflammatory diseases are rheumatoid arthritis or inflammatory bowel diseases.

122. A vaccine according to claim 121, wherein the inflammatory bowel diseases are Crohn's disease or Colitis Ulcerosa.

H1 123. A vaccine according to claim 109, wherein the viral expression vector is a retroviral expression vector.

124. A vaccine according to claim 110, wherein the vaccine is formulated for subcutaneous, intramuscular, or intradermal administration.

125. The method according to claim 111, wherein the antibodies are monoclonal antibodies.

126. The method of claim 115, wherein the assay is amplified using avidin/biotin conjugation.

127. The human TNFα molecule according to claim 83, wherein the segment of the H strand of the front β-sheet and of the connecting loop to the I strand is the segment of amino acids 132 to 146.

128. The human TNFα molecule according to claim 84, wherein the segment of the H and I strands and the entire connecting loop is the segment of amino acids 132 to 152

129. The human TNFα molecule according to claim 85, wherein the segment of the D strand, at least a segment of the E strand and the entire connecting loop is the segment of amino acids 65 to 79 or 64 to 84.

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130. The human TNFα molecule according to claim 86, wherein the entire C' and C strands and a segment of the D strand is the segment of amino acids 40 to 60.

131. The human TNFα molecule according to claim 87, wherein the segment of the E strand and of the front β-sheet of one or both of the connecting loops is the segment of amino acids 76 to 90.

132. The human TNFα molecule according to claim 91, wherein the epitope is epitope P2 and/or P30.

REMARKS

Claims 77-132 are presented for consideration in the present CPA in place of claims 50-76.

The replacement claims are submitted in order to clarify the differences with the prior art relied on in the rejection under 35 USC 103(a), of record, as detailed below. Newly presented claims 77-97, 104, 105, 110, 118, 119, 124, and 127-130 represent subject matter of claims 50-76, as further supported in the application as originally filed. As recited in present claim 77, the "substitution" in "any one of the strands," recited in claim 50, is now recited as expressly leading to "inactivation of the biological activity of human TNFα," as recited in claim 51 and, further, as described in the specification at page 11, lines 28-32, page 17, line 23 to page 18, line 2, and page 39, lines 22-28.